REMARKS

Claims 1-4, 6, 7, 9-11, 13, 25-28, 30, 31, 33-35, 37, 55, 58 and 59 are pending in the case.

Claims 1-4, 6, 7, 9-11, 13, 25-28, 30, 31, 33-35, 37, 55, 58 and 59 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Wheelhouse *et al.* (U.S. Patent No. 6,087,493; hereafter "*Wheelhouse*") in view of Argyris *et al.* (1999, *J. Biol. Chem.* 274(3):1549-1556; hereafter "*Argyris*").

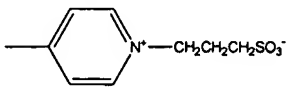
Non-elected claims 14-24, 38-54, 56, 57 and 60-63 are herein cancelled.

Reconsideration of the present application in view of the foregoing amendments and remarks below is respectfully requested.

Claim Rejections under 35 U.S.C. § 103

Claims 1-4, 6, 7, 9-11, 13, 25-28, 30, 31, 33-35, 37, 55, 58 and 59 are rejected under 35 U.S.C. § 103(a) as being unpatentable over *Wheelhouse* in view of *Argyris*.

The Examiner responds to the Applicant's previous argument, stating that "*Wheelhouse* teaches both cationic and negatively charged substituents" and references Table 8, in particular, where R group is:



(B17).

Applicants respectfully traverse the statement and the rejection for the following reasons:

With regard to Table 8, *Wheelhouse* states as follows:

> Table 8 investigated the effect of different pyridine-N-alkyl substituents. In all cases where the positive charge was maintained there was little effect in activity across the series Me, Et, hydroxyethyl, acetoxymethyl. However, ***the two compounds resulting in zwitterions, and hence zero net charge, showed no activity*** under the conditions used. (col. 53, lines 28-34; emphasis added).

Thus, although *Wheelhouse* lists Au as one of the possible metals for metalloporphyrins (col. 3, line 17), the data in *Wheelhouse* indeed ***teaches away*** from the present claimed invention by showing that, regardless of the presence of a chelated metal ion and regardless of the types of the chelated metal (if there is one), the telomerase inhibition activity is none as far as the substituent of the porphyrin is neutral or negatively charged.

This observation was further confirmed by *Wheelhouse*'s clear conclusion, found at col. 18, lines 22-32, that the structures of the porphyrins or metalloporphyrins for effective telomerase inhibition should render the following four prerequisites: (1) positively charged substitution; (2) *meso*-position substitution; (3) non-pyrrolic substitution, and (4) the presence of electron withdrawing group(s) as *meso*-substituents.

In contrast, the present Applicant/inventor has demonstrated that ***gold(III) porphyrins 1a-1i possess acute cytotoxicity*** to a panel of cancer cells (*see* Table 4a at page 40 of the present specification). It should be noted that, unlike the compounds of *Wheelhouse*, the present complexes do ***not*** bear positively-charged substituents and the electronegativity of their substitution groups span over a wide range. In addition, [Au(OEP)]Cl (hereafter "1h"), which is a ***non-meo-substituted porphyrin*** also exhibited comparable cytotoxicity to that of the other gold(III) porphyrins.

Thus, it is obvious that simply following *Wheelhouse*'s idea would not have led one skilled in the art to come up with the method for induction of apoptosis of cancer cells as recited in the present claims.

Applicant wishes to emphasize that the rationale of the present Applicant/inventor was to employ porphyrin ligand to stabilize the highly reactive gold(III) ion and hence, to facilitate the gold(III) anticancer activities. This concept is unprecedented in literature and is not obvious over any prior art cited, including *Wheelhouse* and *Argyris*.

In this connection, the Examiner's statement at page 4, lines 10-14, of the Office Action is erroneous. Unlike the Examiner's assertion, there is no description in *Wheelhouse* regarding the ***stabilization of highly reactive gold(III) by employing porphyrin ligand***. Instead, *Wheelhouse* demonstrated that the porphyrins and the metalloporphyrins that carry the four (4) essential features discussed above were able to ***stabilizes the G-tetrads of quadruplex DNA by duplex intercalation***, thereby inhibiting the telomerase activation (*see*, for example, col. 2, lines 54-62; and col. 15, lines 33-65). Again, for the stabilization of the G-tetrads, positively charged substituents are essential (*see* col. 10, lines 40-51), according to *Wheelhouse*.

In contrast, the present inventor has demonstrated that the gold(III) porphyrins without pyridyl and quinolyl-aldehyde substitution ***do not intercalate with DNA***. By means of DNA viscosity measurements (Fig. 10) and gel mobility shift assay of 100-bp DNA ladder (Fig. 11), the present inventor has demonstrated that no increase in viscosity and tailing effect were observed, respectively, upon the addition of gold(III) porphyrin complexes, indicating no occurrence of DNA intercalation. In such circumstances, if one skilled in the art were to apply *Wheelhouse*'s idea, the use of the gold(III) complexes of the present invention would have been expected to give negative results (*i.e.*, no telomerase inhibition and, hence, no anti-cancer activities). Thus, again,

Wheelhouse teaches away from the gold(III) complexes of the present invention. In contrast, the present inventor has shown that these ***non-DNA intercalating*** gold(III) porphyrins ***do*** possess ***acute cytotoxicity*** (*e.g.*, IC_{50} = 100 nM for the complex "1a" of the present invention) against cancer cells within 48 hours (*see* Table 4a at page 40, of the present specification), which is totally unexpected results in view of *Wheelhouse*, which states that its compounds do ***not*** have such cytotoxicity (*see* col. 16, lines 61-64 of *Wheelhouse*).

Such deficiencies of *Wheelhouse* cannot be cured by combining *Argyris*, either. *Argyris* describes neither anything about the gold(III) complexes of the present invention, nor anything about the anti-cancer cell activities of the disclosed compounds (*i.e.*, heme and zinc protoporphyrin).

Thus, claims 1-4, 6, 7, 9-11, 13, 58 and 59 are not obvious over *Wheelhouse* or *Argyris*, each alone or in combination, and the rejections of these claims under 35 U.S.C. § 102(a) as being unpatentable over *Wheelhouse* in view of *Argyris* should be withdrawn.

With regard to claims 25-28, 30, 31, 33-35, 37 and 55, the Examiner states, in response to the Applicant's previous arguments, that *Argyris* "does not have to teach (Au(III)), the Wheelhouse reference teaches the different metal ions that are capable of such a function (see col. 3, lines 15+) one skilled in the art would have been motivated to substitute Zn for Au and would have expected a successful result in doing so."

Applicant respectfully traverses the statement and the rejection.

The Examiner has ***not*** shown that either or both of the two references contain in themselves any motivation or suggestion for one skilled in the art to combine to each other to obtain the gold(III) complexes of the present invention having an inhibitory activity against HIV-1 reverse transcriptase. This is because, on one hand,

Wheelhouse does not teach at all that the compounds disclosed in *Wheelhouse* have any inhibitory activity against HIV-1 reverse transcriptase. All *Wheelhouse* discloses is a mechanism by which these compounds inhibit telomerase activity, which mechanism being the intercalation of the G-tetrads of quadruplex DNA by these complexes. There is no suggestion in *Wheelhouse* as to how such interactions between these compounds, in particular, gold (III) complexes, and telomerase via G-quadruplex DNA intercalation (which, as demonstrated by the present inventor, does ***not*** actually take place with gold(III) complexes) could be applied to the interactions between these compounds and HIV-1 RT.

On the other hand, *Argyris* discloses that heme and zinc protoporphyrin inhibit HIV-1 and HIV-2 reverse transcriptases (RTs) by binding to the highly conserved region 398-407 of the viral RTs. There is no description in *Argyris* how such specific interactions between HIV-1/HIV-2 RTs and heme or zinc protoporphyrin are applicable to the interactions between these compounds and telomerase.

Thus, the Examiner's assertion that, by combining *Wheelhouse* and *Argyris*, "one skilled in the art would have been motivated to substitute Zn [of *Argyris*] for Au [of *Wheelhouse*] and would have expected a successful result in doing so", is based on impermissible hindsight based on the disclosure of the present invention.

Even, *in arguendo*, *Wheelhouse* and *Argyris* were to be combined, the results would not have been the gold(III) complexes or the method of using them, of the present invention, because, as discussed above, the gold(III) complexes of the present invention: (i) do ***not*** carry positively charged substituents that are essential to the compounds of *Wheelhouse*; and (ii) have ***high acute toxicity***, as opposed to low toxicity of the compounds of *Wheelhouse*. Thus, neither of the references provides reasonable expectation of success.

Accordingly, claims 25-28, 30, 31, 33-35, 37 and 55 are not obvious at all over *Wheelhouse* or *Argyris*, each alone or in combination and, therefore, the rejections of these claims under 35 U.S.C. § 103(a) as being unpatentable over *Wheelhouse* in view of *Argyris* should be withdrawn.

In view of the foregoing amendments and the remarks, Applicant believes that all the pending claims are now in condition for allowance, an early notification of which is respectfully requested.

No fee is believed to be due for this submission. Should any fees be required, please charge such fees to Deposit Account No. 50-2215.

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Respectfully submitted,

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